Considerations for Antiretroviral Use in Special Patient Populations

ACUTE HIV INFECTION (Updated January 10, 2011)

Panel's Recommendations:

- ***It is unknown if treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients with HIV seroconversion in the previous 6 months (CIII).***
- ***All pregnant women with acute or recent HIV infection should start a combination antiretroviral (ARV) regimen as soon as possible to prevent mother-to-child transmission (MTCT) of HIV (AI).***
- ***If the clinician and patient elect to treat acute HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (AIII).***
- ***For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will be helpful in guiding the selection of an ARV regimen that can provide the optimal virologic response; this strategy is therefore recommended (AIII). If therapy is deferred, genotypic resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (AIII).***
- ***Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in antiretroviral therapy (ART)-naïve persons who harbor drug-resistant virus, a ritonavir (RTV)-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

An estimated 40%–90% of patients acutely infected with HIV will experience symptoms of acute retroviral syndrome characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias, and other symptoms *[1-6]*. However, acute HIV infection is often not recognized by primary care clinicians because symptoms are similar to those for influenza, infectious mononucleosis, or other illnesses. Additionally, acute infection can occur asymptomatically. **Table 10** provides practitioners with guidance on the recognition, diagnosis, and management of acute HIV infection.

Diagnosis of Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV infection in patients who have a compatible clinical syndrome and who report recent high-risk behavior *[7]*. However, in some settings, patients may not always disclose or admit to high-risk behaviors or might not perceive their behaviors as high risk. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high-risk behaviors.

When acute retroviral syndrome is suspected, a plasma HIV RNA test is typically used in conjunction with an HIV antibody test to diagnose acute infection **(BII)**. Acute HIV infection is often defined by detectable HIV RNA in plasma in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test because values in acute infection are generally very high (>100,000 copies/mL) *[5-6]*. A qualitative HIV RNA test can also be used in this setting. Interest in routine screening for antibody-negative acute infection has led to select centers performing virologic testing on all antibody-negative specimens, including the use of pooled HIV RNA testing on all seronegative serum samples *[8]*. In addition, a combination HIV antigen/antibody test (ARCHITECT), recently licensed by the Food and Drug Administration (FDA), could be used for this purpose. Patients

diagnosed with acute HIV infection by a virologic test while still antibody negative or indeterminate should have confirmatory serologic testing performed over the next 3 months **(AI)**. (See **Table 10**.)

Performance of Resistance Testing

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one ARV drug in 6%–16% of patients *[9-11]*. If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline to guide the selection of an ARV regimen will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. (See **Drug-Resistance Testing**.) If therapy is deferred, resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.

Treatment for Acute HIV Infection

Clinical trials information regarding treatment of acute HIV infection is limited. Ongoing trials are addressing the question of the long-term benefit of potent treatment regimens initiated during acute infection. Potential benefits and risks of treating acute infection are as follows:

- **Potential Benefits of Treating Acute Infection.** Preliminary data indicate that treatment of acute HIV infection with combination ART has a beneficial effect on laboratory markers of disease progression *[12-16]*. Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk of viral transmission during this highly infectious stage of disease. Additionally, although data are limited and the clinical relevance is unclear, the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection may be mitigated by the early initiation of ART *[17-18]*.
- **Potential Risks of Treating Acute HIV Infection.** The potential disadvantages of initiating therapy include exposure to ART without a known clinical benefit, which could result in drug toxicities, development of drug resistance, continuous need for therapy with strict adherence, and adverse effect on quality of life.

Some of the potential benefits associated with treatment during acute infection remain uncertain and of unknown clinical relevance, while the risks are largely consistent with those for initiating therapy in chronically infected asymptomatic patients with high CD4 counts. The health care provider and the patient should be fully aware that the rationale for therapy for acute HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. For these reasons, treatment of acute HIV infection should be considered optional at this time **(CIII).** Because acute or recent HIV infection is associated with a high risk of MTCT of HIV, all HIV-infected pregnant women should start a combination ARV regimen as soon as possible to prevent perinatal transmission of HIV **(AI)** *[19]*. Following delivery, considerations regarding continuation of the ARV regimen as therapy for the mother are the same as for treatment of other nonpregnant individuals. Providers should consider enrolling patients with acute HIV infection in a clinical trial to evaluate the natural history of acute HIV and to determine the role of ART in this setting. Information regarding such trials can be obtained at **www.clinicaltrials.gov** or from local HIV treatment experts.

Treatment for Recent but Nonacute HIV Infection or Infection of Undetermined Duration

In addition to patients with acute HIV infection, some HIV clinicians also recommend consideration of therapy for patients in whom seroconversion has occurred within the previous 6 months **(CIII)**. Although the initial burst of viremia among infected adults usually resolves in 2 months, rationale for treatment during the 2- to 6-month period after infection is based on the probability that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time *[20]*. In the case of pregnancy, use of a combination ARV regimen to prevent MTCT of HIV is recommended **(AI)**. For nonpregnant patients the current guidelines have provided a rationale for recommending initiation of ART in ART-naïve patients with CD4 count between 350 and 500 cells/mm^3 as well as a recommendation to consider therapy for those with CD4 count >500 cells/mm^3. (See **Initiating Antiretroviral Therapy**.) Although these recommendations are primarily based upon data from patients with chronic infection, the potential benefit of early treatment on immune recovery and on attenuation of the pathologic effects of viremia-associated inflammation and coagulation could apply to those with early HIV infection as well. Based upon all of

these considerations it is reasonable that clinicians share with patients the potential rationale for initiating ART during early HIV infection and offer treatment to those who are willing and able to commit to lifelong treatment.

Treatment Regimen for Acute or Recent HIV Infection

If the clinician and patient have made the decision to initiate ART for acute or recent HIV infection, the goal of therapy is to suppress plasma HIV RNA levels to below detectable levels **(AIII)**. Data are insufficient to draw firm conclusions regarding specific drug combinations to use in acute HIV infection. Potential combinations of agents should be those used in chronic infection. (See **What to Start**.) However, because clinically significant resistance to PIs is less common than resistance to NNRTIs in ART-naïve persons, an RTV-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available **(AIII)**. If resistance test results or resistance pattern of the source virus are known, this information should be used to guide the selection of the ARV regimen.

Patient Follow-up

Testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described in **Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy** (i.e., HIV RNA at initiation of therapy, after 2–8 weeks, then every 4–8 weeks until viral suppression, then every 3–4 months thereafter) **(AII)**.

Duration of Therapy for Acute or Recent HIV Infection

The optimal duration of therapy for patients with acute or recent HIV infection is unknown, but ongoing clinical trials may provide relevant data regarding these concerns. Difficulties inherent in determining the optimal duration and therapy composition for acute or recent infection (and the potential need for lifelong treatment) should be considered when counseling patients prior to initiation of therapy. Patients need to know that there are limited data regarding the benefits of stopping treatment, whereas strong data from studies in patients with chronic HIV infection show that stopping ART may be harmful *[21]*.

Table 10. Identifying, Diagnosing, and Managing Acute HIV-1 Infection (Updated January 10, 2011)

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2–6 weeks) high risk of exposure to HIV*
  - Signs/symptoms/laboratory findings may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.
  - High-risk exposures include sexual contact with a person infected with HIV or at risk of HIV, sharing of injection drug use paraphernalia, or contact of potentially infectious blood with mucous membranes or breaks in skin.*

- **Differential diagnosis:** Epstein-Barr virus (EBV)- and non-EBV (e.g., cytomegalovirus [CMV])-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis

- **Evaluation/diagnosis of acute/primary HIV infection**
  - HIV antibody enzyme immunoassay (EIA) (rapid test if available)
    - Reactive EIA must be followed by Western blot.
    - Negative EIA or reactive EIA with negative or indeterminate Western blot should be followed by a virologic test.†
  - Positive virologic test† in this setting is consistent with acute HIV infection.
  - When acute HIV infection is diagnosed by a positive virologic test (such as HIV RNA or p24 antigen) that was preceded by a negative HIV antibody test, a confirmatory HIV antibody test should be performed over the next 3 months to confirm seroconversion.

- **Considerations for antiretroviral therapy:**
  - All pregnant women with acute or recent HIV infection should start on a combination ARV regimen as soon as possible because of the high risk of MTCT of HIV **(AI)**.
  - Treatment of acute and early HIV infection in nonpregnant persons is considered optional **(CIII)**.
  - Potentially unique benefits associated with ART during acute and early infection exist, although they remain unproven.
  - The risks of ART during acute and early infection are consistent with those for initiating ART in chronically infected asymptomatic patients with high CD4 counts.
  - If therapy is initiated, the goal should be for maintenance of maximal viral suppression.
  - Enrollment in a clinical trial should be considered.

* In some settings, behaviors conducive to acquisition of HIV infection might not be ascertained or might not be perceived as "high risk" by the health care provider or the patient or both. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high-risk behaviors.

† p24 antigen or HIV RNA assay. The p24 antigen is less sensitive but more specific than HIV RNA tests; HIV RNA tests are generally preferred. HIV RNA tests include quantitative branched DNA (bDNA), reverse transcriptase-polymerase chain reaction (RT-PCR), or qualitative transcription-mediated amplification (APTIMA, GenProbe).

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HIV-INFECTED ADOLESCENTS AND YOUNG ADULTS (Updated January 10, 2011)

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 15% of the 35,314 new HIV diagnoses reported among the 33 states that participated in confidential, name-based HIV infection reporting in 2006 were among youth 13–24 years of age *[1]*. Recent trends in HIV prevalence reveal that the disproportionate burden of HIV/AIDS among racial minorities is even greater among youth 13–19 years of age than among young adults 20–24 years of age *[2]*. Furthermore, trends for all HIV/AIDS diagnoses in 33 states from 2001 to 2006 decreased for all transmission categories except among men who have sex with men (MSM). Notably, among all black MSM, the largest increase in HIV/AIDS diagnoses occurred among youth 13–24 years of age *[3]*. HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications should be used.

Most adolescents who acquire HIV are infected through high-risk behaviors. Many of them are recently infected and unaware of their HIV infection status. Thus, many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage, and engagement to care. A recent study among HIV-infected adolescents and young adults presenting for care identified primary genotypic resistance mutations to ARV medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing *[4]*. This transmission dynamic reflects that a substantial proportion of youth's sexual partners are likely older and may be more ART experienced; thus, awareness of the importance of baseline resistance testing among recently infected youth naïve to ART is imperative.

A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or in infancy through blood products. Such adolescents are usually heavily ART experienced and may have a unique clinical course that differs from that of adolescents infected later in life *[5]*. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be based on the same guiding principles as for heavily ART-experienced adults. (See **Virologic and Immunogic Failure**.)

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and compete with concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and the need to "fit in" with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage them in care so they can improve and maintain their health for the long term.

Antiretroviral Therapy Considerations in Adolescents

Adult guidelines for ART are usually appropriate for postpubertal adolescents, because the clinical course of HIV-infected adolescents who were infected sexually or through injection drug use during adolescence is more similar to that of adults than to that of children. Adult guidelines can also be useful for postpubertal youth who were perinatally infected because these patients often have treatment challenges associated with the use of long-term ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects.

Dosage of medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not solely on the basis of age *[6-7]*. Adolescents in early puberty (i.e., Tanner Stages I and II) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in children who were infected with HIV perinatally *[8]*, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each ARV medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt period (i.e., Tanner Stage III in females and Tanner Stage IV in males) and following adult or pediatric dosing guidelines and adolescents

who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in selected circumstances to help guide therapy decisions in this context. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see ***Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*** *[9]*.

Adherence Concerns in Adolescents

HIV-infected adolescents are especially vulnerable to specific adherence problems based on their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health care systems and who lack health insurance. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include:

- denial and fear of their HIV infection;
- misinformation;
- distrust of the medical establishment;
- fear and lack of belief in the effectiveness of medications;
- low self-esteem;
- unstructured and chaotic lifestyles;
- mood disorders and other mental illness;
- lack of familial and social support;
- absence of or inconsistent access to care or health insurance; and
- incumbent risk of inadvertent parental disclosure of the youth's HIV infection status if parental health insurance is used.

In selecting treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ART regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., beepers, timers, and pill boxes) that are stylish and inconspicuous *[10]*. It is important to make medication adherence as user friendly and as little stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers *[11-13]*. Directly observed therapy might be considered for selected HIV-infected adolescents such as those with mental illness *[14-18]*.

Difficult Adherence Problems

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. The ability of youth to adhere to therapy needs to be included as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for HIV-infected adolescents frequently manage youth who, while needing therapy, pose significant concerns regarding their ability to adhere to therapy. In these cases, alternative considerations to initiation of therapy can be the following: (1) a short-term deferral of treatment until adherence is more likely or while adherence-related problems are aggressively addressed; (2) an adherence testing period in which a placebo (e.g., vitamin pill) is administered; and (3) the avoidance of any regimens with low genetic resistance barriers. Such decisions are ideally individualized to each patient and should be made carefully in context with the individual's clinical status. For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents, see ***Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection*** *[9]*.

Special Considerations in Adolescents

Sexually transmitted infections (STIs), in particular human papilloma virus (HPV), should also be addressed in all adolescents. For a more detailed discussion on STIs, see the most recent CDC guidelines *[19]* and the pediatric opportunistic infection treatment guidelines on HPV among HIV-infected adolescents *[20]*. Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce risks, should be provided to all youth. Providing gynecologic care for the HIV-infected female adolescent is especially important. Contraception, including the interaction of specific ARV drugs on hormonal contraceptives, and the potential for pregnancy also may alter choices of ART. As an example, efavirenz (EFV) should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see **HIV-Infected Women** and the ***Perinatal Guidelines*** *[21]*.

Transitioning Care

Given lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for HIV-infected children, adolescents, and young adults. A successful transition requires an awareness of some fundamental differences between many adolescent and adult HIV care models. In most adolescent HIV clinics, care is more "teen-centered" and multidisciplinary, with primary care being highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as medical insurance, independence, autonomy, decisional capacity, confidentiality, and consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients. As an additional complication to this transition, HIV-infected adolescents belong to two epidemiologically distinct subgroups: (1) those perinatally infected—who would likely have more disease burden history, complications, and chronicity; less functional autonomy; greater need for ART; and higher mortality risk; and (2) those more recently infected due to high-risk behaviors. Thus, these subgroups have unique biomedical and psychosocial considerations and needs.

To maximize the likelihood of a successful transition, facilitators to successful transitioning are best implemented early on. These include the following: (1) optimizing provider communication between adolescent and adult clinics; (2) addressing patient/family resistance caused by lack of information, stigma or disclosure concerns, and differences in practice styles; (3) preparing youth for life skills development, including counseling them on the appropriate use of a primary care provider and appointment management, the importance of prompt symptom recognition and reporting, and the importance of self-efficacy with medication management, insurance, and entitlements; (4) identifying an optimal clinic model for a given setting (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in); (5) implementing ongoing evaluation to measure the success of a selected model; (6) engaging in regular multidisciplinary case conferences between adult and adolescent care providers; (7) implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; and (8) incorporating a family planning component into clinical care. Attention to these key areas will likely improve adherence to appointments and avert the potential for a youth to "fall through the cracks," as it is commonly referred to in adolescent medicine.

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HIV AND ILLICIT DRUG USERS (IDUs) (Updated January 10, 2011)

Treatment Challenges of HIV-Infected IDUs

Injection drug use is the second-most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate). The most commonly used illicit drugs associated with HIV infection are heroin and stimulants (e.g., cocaine and amphetamines); however, the use of club drugs has increased substantially in the past several years and is common among those who have HIV infection or who are at risk of HIV infection. Methamphetamine and amyl nitrate (i.e., poppers) have been the most strongly associated with high-risk sexual behavior in men who have sex with men (MSM), and the association is less consistent with the other club drugs *[1]*.

All illicit drugs have been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection because depression is one of the strongest predictors of poor adherence and poor treatment outcomes *[2]*. Although treatment of HIV disease in this population can be successful, IDUs who have HIV disease present special treatment challenges. These may include the following: (1) an array of complicating comorbid medical and mental health conditions; (2) limited access to HIV care; (3) inadequate adherence to therapy; (4) medication side effects and toxicities; (5) the need for substance abuse treatment; and (6) drug interactions that can complicate HIV treatment *[3]*.

Underlying health problems among injection and noninjection drug users result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in IDUs with HIV disease, due in part to respiratory, hepatic, and neurological impairments *[4]*. Successful HIV therapy for IDUs often rests upon acquiring familiarity with and providing care for these comorbid conditions and overdose prevention support.

IDUs have less access to HIV care and are less likely to receive antiretroviral therapy (ART) than other populations *[5-6]*. Factors associated with low rates of ART among IDUs include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and lack of expertise among health care providers *[5-6]*. The typically unstable, chaotic life patterns of many IDUs; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence *[7]*. The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and IDUs *[8-9]*. The first step in provision of care and treatment for these individuals is to recognize the existence of a substance abuse problem. Whereas this is often open and obvious, patients may hide such behaviors from clinicians. Assessment of a patient for substance abuse should be part of routine medical history taking and should be done in a clinical, straightforward, and nonjudgmental manner.

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although IDUs are underrepresented in HIV therapy clinical trials, available data indicate that—when they are not actively using drugs— efficacy of ART in IDUs is similar to that seen in other populations *[10]*. Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use *per se [11]*. Providers need to remain attentive to the possible impact these factors have upon the patient before and during prescription of ART. Although many IDUs can sufficiently control their drug use over long enough periods of time to benefit from care**,** substance abuse treatment is often necessary for successful HIV management.

Close collaboration with substance abuse treatment programs and proper support and attention to this population's special multidisciplinary needs are critical components of successful HIV treatment. Essential to this end are accommodating and flexible, community-based HIV care sites that are characterized by familiarity with and

nonjudgmental expertise in management of drug users' wide array of needs and in development of effective strategies to promote medication adherence *[9]*, including, if available, the use of adherence support mechanisms such as modified directly observed therapy, which has shown promise in this population *[12]*.

Antiretroviral Agents and Opioid Substitution Therapy

IDUs are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal, and hematologic disorders are highly prevalent among IDUs. Selection of ARV agents in this population should be made with consideration of these comorbid conditions. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended release naltrexone are commonly used for management of opioid dependence in HIV-infected patients.

Methadone and ART. Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur *[13]*. These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of this interaction. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved.

Buprenorphine and ART. Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is being increasingly used for opioid dependence treatment. The lower risk of respiratory depression and overdose compared with methadone allows it to be prescribed by physicians in primary care for the treatment of opioid dependency. This flexible treatment setting could be of significant value to opioid-addicted HIV-infected patients who require ART because it enables one physician or program to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and antiretroviral agents *[13-14]*. Findings from available studies show a more favorable drug interaction profile than that of methadone.

Naltrexone and ART. A once monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP 450 enzyme system and is not expected to interact with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) *[15]*.

Table 11 provides the currently available pharmacokinetic interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine. Particular attention is needed concerning communication between HIV care providers and drug treatment programs regarding additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP 450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported *[16]*.

Summary

It is usually possible over time to support most active drug users such that acceptable adherence levels with ARV agents can be achieved *[17-18]*. Providers must work to combine all available resources to stabilize an active drug user in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment, needle and syringe exchange, reduction in high-risk sexual behavior, and harm reduction strategies. A

history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to individuals who do not abuse drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include supportive clinical sites; linkage to substance abuse treatment; and awareness of the interactions between illicit drugs and ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (January 10, 2011)

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine* AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ATV	buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible Do not coadminister buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect, norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71% No dose adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80%; TPV C_{min} ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, FPV +/- RTV, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction

Concomitant Drug	Antiretroviral Class/Drug	Pharmacokinetic Interactions Recommendations/Clinical Comments
Methadone	ABC	methadone clearance ↑ 22% No dosage adjustment necessary.
	d4T	d4T AUC ↓ 23% and C_{max} ↓ 44% No dosage adjustment necessary.
	ZDV	ZDV AUC ↑ 29%–43% Monitor for ZDV-related adverse effects.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.
	NVP	methadone AUC ↓ 41% NVP: no significant effect Opioid withdrawal common; increased methadone dose often necessary.
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	With ATV/r, DRV/r, FPV/r: R-methadone[†] AUC ↓ 16%–18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1,000/100mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone C_{min} ↓ 21%, AUC no significant change Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose.
	ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL	No significant effect No dosage adjustment necessary.
	FTC, MVC, T20	No data

[*] Norbuprenorphine is an active metabolite of buprenorphine.
[†] R-methadone is the active form of methadone.

Acronyms: 3TC = lamivudine, d4T = stavudine, T20 = enfuvirtide, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ritonavair, ddI = didanosine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

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HIV-INFECTED WOMEN (Updated January 10, 2011)

Panel's Recommendations:

- ***The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents (AI).***
- ***Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended pregnancy (AIII).***
- ***In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Genotypic resistance testing is recommended for all HIV-infected persons, including pregnant women, prior to initiation of ART (AIII) and for women entering pregnancy with detectable HIV RNA levels while on therapy (AI).***
- ***When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Efavirenz (EFV) should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception (AIII).***
- ***Clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines when designing a regimen for a pregnant woman (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

This section provides discussion of some basic principles and unique considerations to follow when caring for HIV-infected women in general and for pregnant HIV-infected women. Clinicians who provide care for pregnant women should consult the current ***Perinatal Guidelines*** *[1]* for in-depth discussion and management assistance.

Gender Considerations in Antiretroviral Therapy

In general, studies to date have not shown differences in virologic efficacy of ART by gender *[2-4],* although a number of studies have suggested that gender or sex may influence the frequency, presentation, and severity of selected ARV-related adverse events *[5]*. Although data are limited, there is also evidence that women may metabolize and respond to specific medications, including ARV drugs, differently than men *[6-8]***.**

Adverse Effects:

- ***Nevirapine (NVP)-associated hepatotoxicity***: NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among ARV-naïve individuals; women with higher CD4 counts (>250 cells/mm^3) appear to be at greatest risk *[9-12]*. It is generally recommended that NVP not be prescribed to ARV-naïve women who have CD4 counts >250 cells/mm^3 unless there is no other alternative and the benefit from NVP outweighs the risk of hepatotoxicity **(AI)**.
- ***Lactic acidosis***: There appears to be a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside reverse transcriptase inhibitors (NRTIs). Lactic acidosis is most common with stavudine (d4T), didanosine (ddI), and zidovudine (ZDV); however, it can occur with other NRTIs *[13]*.
- ***Metabolic complications***: A few studies have compared women to men in terms of metabolic complications associated with ARV use. HIV-infected women are more likely to experience increases in central fat with ART and are less likely to have triglyceride elevations on treatment *[14-15]*. Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and ART *[16-17]*. At the present time, none of these differences requires a change in recommendations regarding treatment or monitoring.

Women of Childbearing Potential

All women of childbearing potential should be offered preconception counseling and care as a component of routine primary medical care. Discussion should include special considerations with ARV use when trying to conceive and during pregnancy. (See ***Perinatal Guidelines*** *[1]*). The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception to prevent unintended pregnancy should be discussed with women. As part of the evaluation for initiating ART, women should be counseled about the potential teratogenic risk of EFV-containing regimens, should pregnancy occur. EFV-containing regimens should be avoided in women who are trying to conceive or who are sexually active and not using effective and consistent contraception.

Effective contraception should be available for women who wish to prevent pregnancy. Several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have drug interactions with combined oral contraceptives (COCs). Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see **Tables 15a and b**), which potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects (e.g., thromboembolic risk). In general, women who are on any of these ARV drugs should use an alternative or additional method of contraception **(AIII)**. Although there is minimal information about drug interactions with use of newer combined hormonal contraceptive methods (e.g., transdermal patch, vaginal ring), an additional or alternative contraceptive method should also be considered on the basis of established drug interactions between ARVs and COCs. Data on drug interactions between ARVs and progestin-only contraceptive methods are limited; however, recent data have found no significant changes in ARV drug concentrations of nelfinavir (NFV), NVP, or EFV when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness *[18-20]*. Intrauterine devices have been shown to be safe and effective in HIV-infected women *[21-22]*. Counseling about reproductive issues should be provided on an ongoing basis.

Pregnant Women

The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic, or clinical parameters, primarily for prevention of HIV transmission from mother to child and for treatment of maternal infection **(AI)**. Pregnant HIV-infected women should be counseled regarding the known benefits versus potential risks of ARV use during pregnancy to the mother, fetus, and newborn. A woman's decision regarding ARV use should be respected. Coercive and punitive policies undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize maternal, fetal, and neonatal well-being.

Prevention of Mother-to-Child Transmission (PMTCT). Both reduction of HIV RNA levels and use of ARVs appear to have an independent effect on reduction of perinatal transmission of HIV *[23-25]*. The goal of ARV use is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy, but most critically by late pregnancy and the time of delivery, when most transmission occurs.

Genotypic resistance testing is recommended for all pregnant women prior to ARV initiation **(AIII)** and for women entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Optimal prevention of perinatal transmission may require initiation of ARV before results of resistance testing are available. If results demonstrate the presence of significant mutation(s) that may confer resistance to the prescribed ARV regimen, the regimen should be modified.

Long-term follow-up is recommended for all infants born to women who have received ARVs during pregnancy, regardless of the infant's HIV status.

Regimen Considerations. Pregnancy should not preclude the use of optimal drug regimens. However, recommendations regarding the choice of ARVs for treatment of HIV-infected pregnant women are subject to unique considerations, which may result in different specific recommendations regarding timing of initiation and choice of drugs. These considerations include the following:

- potential changes in pharmacokinetics, and thus dosing requirements, which result from physiologic changes associated with pregnancy,
- potential ARV-associated adverse effects in pregnant women,
- effect on the risk of perinatal transmission of HIV, and
- potential short- and long-term effects of the ARV on the fetus and newborn, which are unknown for many drugs.

Clinicians should review the ***Perinatal Guidelines*** *[1]* for a detailed discussion of drug choices. Combination drug regimens are considered the standard of care in pregnancy, both for the treatment of HIV infection and for PMTCT. ZDV by intravenous infusion to the mother during labor and orally to the neonate for 6 weeks is recommended irrespective of antenatal regimen chosen.

There are some specific differences in treatment recommendations in pregnancy based on the above considerations.

NRTIs:

- Although no longer considered a preferred NRTI for non-pregnant adults and adolescents, ZDV is still one of the preferred NRTI drugs when used in pregnancy based on long-term effectiveness in prevention of transmission and safety data in pregnancy (for more detailed discussion, see the ***Perinatal Guidelines*** *[1]*). However, ZDV should not be included in a regimen if there is severe toxicity, documented resistance, or if the woman is also receiving d4T. Women already on a fully suppressive regimen that does not include ZDV should continue on the regimen **(AIII)**.
- The syndrome of lactic acidosis and hepatic steatosis may present with similar signs and symptoms to certain pregnancy-specific disorders (i.e., acute fatty liver of pregnancy, HELLP [hemolysis, elevated liver enzymes, low platelet count] syndrome). Given this similarity, clinicians should have a low threshold for considering lactic acidosis in the differential diagnosis and for appropriate evaluation of pregnant HIV-infected women receiving NRTIs with a consistent clinical picture, particularly if they have accompanying hepatitis or pancreatitis.

NNRTIs:

- EFV-containing regimens **should be avoided** in the first trimester, because significant teratogenic effects were seen in primate studies at drug exposures similar to those achieved during human exposure **(AIII)**. In addition, several cases of neural tube defects have now been reported after early human gestational exposure to EFV *[26-27]*. EFV may be considered for use after the first trimester if indicated because of toxicity, resistance, drug interaction issues, or other clinical concerns (e.g., adherence, presentation after first trimester on EFV-containing regimen) *[28]*.
- Although there is no evidence that pregnancy additionally increases risk of NVP toxicity over that in nonpregnant women *[29]*, NVP should not be initiated as a component of a combination regimen in ARV-naïve pregnant women who have CD4 counts >250 cells/mm^3 unless the benefit clearly outweighs the risk **(AII)**.

PIs:

- Several small studies show that optimal levels of several PIs may not be achieved in pregnancy with standard dosing, especially in the third trimester, although the clinical relevance of this is unknown *[30-32]*. For more information regarding potential dosing alterations, please refer to the ***Perinatal Guidelines*** *[1]*. Once-daily lopinavir/ritonavir (LPV/r) dosing is not recommended in pregnancy, because there are no data to address adequacy of blood levels with this dosing regimen **(BII)**.

Minimal data exist on the use of newer agents, including entry inhibitors and integrase inhibitors, in pregnancy.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (**http://www.apregistry.com**). The registry collects observational data regarding exposure to FDA-approved ARV drugs during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of ART during pregnancy, refer to the ***Perinatal Guidelines*** *[1]*. Lastly, women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for nonpregnant adults and adolescents.

Discontinuation of Antiretroviral Therapy Postpartum

Following delivery, considerations regarding continuation of ART for maternal therapeutic indications are the same as for other nonpregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference. A study from the Women and Infants Transmission Study (WITS) of women who were ARV naïve prior to pregnancy and had CD4 counts >350/mm^3 *[33]* found no significant differences in CD4 count, viral load, or disease progression among those who did or did not continue ART after delivery through 12 months postpartum. In most cases, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, if therapy includes an NNRTI, stopping all regimen components simultaneously may result in functional monotherapy because of the long half-life of the NNRTI, which may increase risk of resistance. In one study, NVP resistance was identified in 16% of women on an NVP-containing regimen despite continuation of the NRTI backbone for 5 days after stopping NVP *[34]*. For women whose antepartum regimen included an NNRTI and who plan to stop ARV prophylaxis after delivery, consideration should be given to stopping the NNRTI and continuing the other ARV or switching from an NNRTI to a PI prior to interruption and continuing the PI with the other ARV for a period of time before electively stopping ART. The optimal interval between stopping an NNRTI and the other ARV is not known; at least 7 days is recommended but some experts recommend continuing the other ARV or substituting a PI plus two other agents for up to 30 days. Additional research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens after delivery in situations when ongoing maternal treatment is not indicated and to assess the effect of limited-duration, fully suppressive ARV prophylaxis in pregnancy on future treatment efficacy. (See **Discontinuation or Interruption of Antiretroviral Therapy**.)

In HIV and hepatitis B virus (HBV) coinfected pregnant women who are receiving ART only for perinatal prophylaxis and who are stopping therapy after delivery, careful clinical and laboratory monitoring for HBV flare should be performed postpartum when ARVs active against HBV are discontinued. However, if treatment for HBV is indicated, a full combination regimen for both HIV and HBV infection should be continued. (See **Initiating Antiretroviral Therapy**.)

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HIV-2 INFECTION (Updated January 10, 2011)

HIV-2 infection is endemic in West Africa. Although HIV-2 has had only limited spread outside this area, it should be considered in persons of West African origin or those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high in countries with strong socioeconomic ties to West Africa (e.g., France; Spain; Portugal; and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India near Goa).

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rates compared with HIV-1 infection *[1-2]*. However, HIV-2 infection can progress to AIDS, and thus antiretroviral therapy (ART) may become necessary during the course of infection. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from an area with high prevalence of HIV-2. In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot) *[3]*. The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable viral loads or in those with declining CD4 counts despite apparent virologic suppression on ART.

The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is Food and Drug Administration (FDA) approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2, and no HIV-2 commercial viral load assays are currently available *[4-5]*. Most studies reporting HIV-2 viral loads use "in-house" assays that are not widely available, making it difficult to monitor virologic response in the clinical setting. In addition, no validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are available.

To date, there have been no randomized trials addressing the question of when to start ART or the choice of initial or second-line therapy for HIV-2 infection *[6]*; thus, the optimal treatment strategy has not been defined. HIV-2 appears intrinsically resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) *[7]* and to enfuvirtide *[8]*. *In vitro* data suggest HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1 *[9-10]*. Variable sensitivity among protease inhibitors (PIs) has been reported; lopinavir (LPV), saquinavir (SQV), and darunavir (DRV) are more active against HIV-2 than other approved PIs *[11-14]*. The integrase inhibitor, raltegravir (RAL) *[15]*, and the CCR5 antagonist, maraviroc (MVC), appear active against some HIV-2 isolates, although no approved assays to determine HIV-2 coreceptor tropism exist and HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4 *[16]*. Several small studies suggest poor responses among HIV-2 infected individuals treated with some ARV regimens, including dual-NRTI regimens, regimens containing two NRTIs + NNRTI, and some unboosted PI-based regimens including nelfinavir (NFV) or indinavir (IDV) plus zidovudine (ZDV) and lamivudine (3TC) *[6, 17-19]*. Clinical data on the utility of triple-NRTI regimens are conflicting *[20-21]*. In general, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses *[21]*. One small study suggested satisfactory responses to lopinavir/ritonavir (LPV/r)-containing regimens in 17 of 29 (59%) of ARV-naïve subjects *[22]*.

Resistance-associated mutations develop commonly in HIV-2 patients on therapy *[17, 21, 23]*. Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathways and mutational patterns leading to resistance may differ *[10, 21, 24]*. CD4 cell recovery on therapy may be poor *[25]*, suggesting that more reliable methods for monitoring disease progression and treatment efficacy in HIV-2 infection are needed.

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection *[24]*, though as yet there are no controlled trial data to reliably predict their success. Until more definitive data are available in an ART-naïve patient with HIV-2 mono-infection or with HIV-1/HIV-2 dual infection who requires treatment, clinicians should initiate a regimen containing two NRTIs and a boosted PI. Monitoring of virologic response in such patients is problematic because of the lack of a commercially available HIV-2 viral load assay; however, clinical and CD4 count improvement can be used to assess treatment response.

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